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SYNTHESIS OF NOVEL C-4 DISUBSTITUTED β-LACTAMS THROUGH STAUDINGER CYCLOADDITION REACTION

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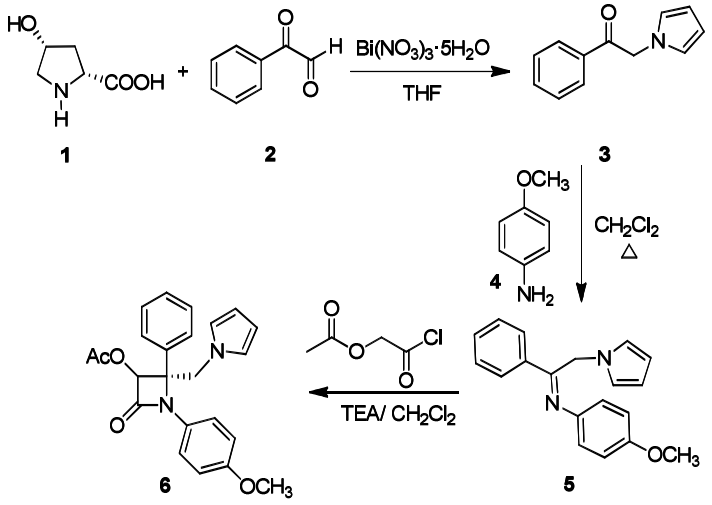
Abstract: Synthesis of novel C-4 disubstituted beta-lactam that has N-methyl pyrrole system has been achieved through Staudinger cycloaddition reaction of acid chloride and imine. Interestingly, this reaction has produced a single stereoisomer.

Key words: Cycloaddition, Imine, Pyrrole, β-Lactam

Introduction: Reaction of imines with activated acid chlorides (or its equivalent) is called Staudinger cycloaddition reaction and this method produces β-lactam rings with different stereochemistries[1]. Synthesis of β-lactams that have quaternary carbon center at C-3 and C-4 is important objective. It is very difficult to insert a pyrrole in the β-lactams ring system at C-3 or C-4. We have demonstrated synthesis of optically active C-3-pyrrole substituted β-lactam starting from hydroxyproline derivative [2]. Based upon the success of this reaction, our attention has turned to prepare C-4 pyrrole substituted β-lactam ring system following Staudinger cycloaddition reaction. This communication describes the preparation of this type of β-lactam starting from phenyl glyoxal.

Results and Discussions: During the course of investigation of β-lactams, we became aware that aromatic rings are extensively used for the synthesis and biological evaluation of C-3 and C-4-substitutedβ-lactams.However, synthesis of C-4 pyrrole-substituted β-lactams is not known. Pyrroles rings are more basic than phenyl or substituted phenyl rings. Since biological results depend on basicity/acidic nature of organic molecules, we have undertaken synthesis of β-lactams that have a pyrrole unit connected to the C-4 ring of a β-lactam ring through a methylene group. Such basic molecules can be protonated under physiological pH without cleavage of the ring system.
We synthesized pyrrole substituted indole derivatives using hydroxyproline and catalytic amount of bismuth nitrate [3]. A similar reaction of hydroxyproline**1** and phenyl glyoxal**2** in the presence of bismuth nitrate produced pyrrole substituted acetophenone derivative **3**in 90% yieldat reflux temperature (**Scheme 1**).

Scheme 1: Highly Steroselective Synthesis of C-4 Disubstituted β-Lactam



Compound **3** was then converted to the imine **5** in quantitative yield by reacting with para-anisidine **4** at reflux temperature. Imine **5** was treated with acetoxy acetyl chloride in the presence of triethylamine at room temperature. A single β-lactam **6** that has a C-4 quaternary center with N-methyl substituted pyrrole was isolated from the reaction mixture in 65% yield. The stereochemistry of the β-lactam **6** was determined from 2D (NOESY experiment). The steric hindrance and electronic interaction of the C-4 Pyrrole system and C-3 acetoxy group was responsible for this stereochemistry. The electron pair of the one of the oxygens of the acetoxy group and nitrogen of the pyrrole ring favored their *trans*configuration, although we are aware single crystal X-Ray crystallography would be the choice to know the absolute stereochemistry of the β-lactam **6**.

Conclusion: Synthesis of β-lactam derivatives as described herein is novel and this type of structure is unknown. The method is simple, but has diverse potential to create molecules which are not possible to obtain by any other methods. The detail description of this work will be reported in due course.

Experimental: To a solution of hydroxyproline**1** (1.1 mmol) and phenyl glyoxal **2** (1 mmol) in anhydrous THF (5 mL) was added bismuth nitrate (40 mg) and the reaction mixture was stirred for 4h at room temperature. The reaction mixture was extracted with dichloromethane (40 mL), washed with sodium bicarbonate solution (5%, 10 mL), dried with sodium sulfate and evaporated to afford **3** in 90% yield. To the crude oily residue **3** was added para-anisidine **4** (1.1 mmol) in anhydrous dichloromethane (10 mL) and powered molecular sieves (1 gm). The reaction mixture was refluxed for 2h and it was then filtered, washed with dichloromethane (10 mL) and solvent was evaporated to produce imine **5** in quantitative yield. Crude imine **5** was taken in dry dichloromethane (10 mL) and dry triethylamine (3 mmol) was added to it. The reaction mixture was cooled at 0^0C and acetoxyacetyl chloride (1.5 mmol) was added dropwise to it and the reaction mixture was stirred at room temperature overnight. The reaction mixture

was washed with dilute hydrochloric acid (3N, 10 mL), sodium bicarbonate (10%, 10 mL), brine (10 mL), dried with sodium sulfate and solvent was evaporated to afford the crude **6**. The crude product **6** was purified through column chromatography over silica gel and pure product **6** was isolated with ethyl acetate/hexanes (20:80) in 65% yield; semi-solid product; IR (neat): 3400, 3320, 2960, 1750, 1730, 140, 1600, 1558, 1505, 1500 cm-$^{1;1}$H NMR ($CDCl_3$, 300 MH_Z): 7.62-7.33 (5H, Ar), 7.21(2H, Ar), 6.95(2H, Ar), 6.91 (2H, pyrrole), 6.8 (2H, pyrrole), 5.80 (1H, s), 3.85 (3H, s), 3.72 (2H, s), 2.08 (3H, s).

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